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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,535	SULLENGER ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/04/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

5:00

DETAILED ACTION

Double Patenting

1. Claims 1-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,667,969. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 1-7 of U.S. Patent No. 5,667,969 teach a method for splicing a non-viral target nucleic acid molecule within a cell in culture with a separate nucleic acid molecule, wherein said target molecule is deleterious to the cell in which it is located, and wherein said separate nucleic acid molecule is adapted to form a non-deleterious target molecule when spliced with at least a part of said target nucleic acid molecule, comprising the step of: contacting said target nucleic acid molecule with a catalytic nucleic acid molecule comprising said separate nucleic acid molecule under conditions in which at least a portion of said separate nucleic acid molecule is spliced with at least a portion of said target nucleic acid molecule to form said non-deleterious nucleic acid molecule, and wherein said catalytic nucleic acid molecule is active to cleave said target nucleic acid molecule and to splice said separate nucleic acid molecule with said target nucleic acid molecule, and wherein said catalytic nucleic acid molecule is a group I or group II intron molecule and wherein said contacting is in vitro and wherein said target nucleic acid is an RNA molecule and wherein said separate nucleic acid molecule is an RNA molecule and wherein said contacting comprises providing a vector encoding said catalytic nucleic acid molecule comprising said separate nucleic acid molecule.

Claims 1-7 of U.S. Patent No. 5,667,969 represent a species of the more generic claims currently pending which are not limited to performance in culture and which are not limited to formation of a non-deleterious target molecule and the species anticipates the broader generic claims and consequently renders it obvious.

2. Claims 1-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-6 of U.S. Patent No. 5,869,254. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 1-6 of U.S. Patent No. 5,869,254 teach a method for splicing a non-viral target nucleic acid molecule with a separate nucleic molecule comprising a catalytic nucleic acid molecule, wherein said target nucleic acid molecule includes a nucleic acid sequence deleterious to an organism in which it is located, and wherein said separate nucleic acid molecule is adapted to correct said defect after splicing with said target molecule, comprising the step of: contacting said target nucleic acid molecule in a cell in vitro with said separate nucleic acid molecule comprising a catalytic nucleic acid molecule in the presence of one or more spliceosomes or splicing factors under conditions in which at least a portion of said separate nucleic acid molecule is spliced with at least a portion of said target nucleic acid molecule to form a non-deleterious nucleic acid molecule. Also taught is a method wherein said catalytic nucleic acid molecule is active to cleave said target nucleic acid molecule and to splice said separate nucleic acid molecule with said target nucleic acid molecule and wherein said catalytic nucleic acid molecule is a group I or group II intron molecule. Also taught is

wherein said target nucleic acid molecule is an RNA molecule and wherein said contacting comprises providing an expression vector encoding said separate nucleic acid molecule.

Claims 1-6 of U.S. Patent No. 5,869,254 represent a species of the more generic claims currently pending which are not limited defect correction and the species anticipates the broader generic claims and consequently renders it obvious.

3. Claims 1-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-5 of U.S. Patent No. 6,897,016. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 1-5 of U.S. Patent No. 6,897,016 teach a Method for splicing a target RNA molecule comprising a mutant beta-globin nucleotide sequence within a cell in culture with a separate RNA molecule comprising a wild type beta-globin nucleotide sequence, wherein a protein product of the target RNA molecule is deleterious to the cell in which it is located, and wherein the separate RNA molecule is adapted to form a target RNA molecule with the wild type beta-globin nucleotide sequence in place of mutant beta-globin nucleotide sequence when spliced with at least a part of the target RNA molecule, the method comprising: contacting the target RNA molecule with a catalytic RNA molecule comprising the separate RNA molecule, under conditions in which at least a portion of the separate RNA molecule is spliced with at least a portion of the target RNA molecule to form the target RNA molecule with the wild type beta-

globin nucleotide sequence in place of mutant beta-globin nucleotide sequence when spliced with at least a part of the target RNA molecule.

Claims 1-5 of U.S. Patent No. 6,897,016represent a species of the more generic claims currently pending which are not limited defect correction or to Beta globin and the species anticipates the broader generic claims and consequently renders it obvious.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-9, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Haseloff et al (WO 92/13090).

Haseloff teaches a method for splicing a target nucleic acid molecule with a separate nucleic acid molecule comprising the steps of : contacting said target nucleic acid molecule with a catalytic nucleic acid molecule in cells and therefore necessarily in the presence of spliceosomes and splicing factors, comprising a separate nucleic acid molecule such that the separate nucleic acid molecule is spliced to the target molecule to form a chimeric in the presence of one or more spliceosomes where the catalytic nucleic acid molecule which functions to splice is a group I or II intron, which method may be performed in vitro or in vivo and which nucleic acid may be RNA (page 9, line 1 to page 11, line 4 and page 16, line 30 to page 31, line 14). Haseloff further teaches placement of the ribozyme into an expression vector (page 35, lines 9-41).

Haseloff expressly teaches that "The ribozymes or proribozyme of the invention may also be engineered to destroy viruses. In one embodiment, the ribozymes or proribozyme of the invention is provided in a genetically stable manner to a host cell prior to viral attack. Infection by the appropriate virus or expression of the latent virus in such host cell (resulting in the appearance of the ribozyme's or proribozyme target RNA

in the host cell), would stimulate the catalytic activity of the ribozyme and destruction of the viral RNA target and/or production of a toxin via trans-splicing resulting in the death of the virus infected cell (page 32, lines 14-24)". This statement expressly teaches creating a chimeric molecule using a ribozyme with a viral RNA target which target is deleterious to the host cell, which viral RNA is rendered non-deleterious after splicing

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Haseloff as applied to claims 1-9, 11 and 12 and further in view of Weber et al (J. Gen. Virol. (1992) 73:2955-2961).

Haseloff teaches the method of claim 1 as discussed above. Haseloff does not teach a motivation for using a dominant negative allele in the method.

Weber teaches "Dominant negative or trans-dominant mutants of viral proteins represent a new and exciting potential approach to antiviral therapy (abstract)". Weber also teaches "Moreover, a truncated form of ICP0 which can be hypothetically created by alternative splicing was found to possess similar inhibitory properties, suggesting that a virus-encoded version of this dominant negative mutant may play a role in down-regulating HSV-1 gene expression during infection *in vivo* (abstract)".

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the trans-splicing of proteins method of Haseloff with the dominant negative viral mutants of Weber for the reasons expressly stated by Weber as shown above. An ordinary practitioner would have been motivated to combine the teachings of Haseloff with those of Weber for the stated benefits of antiviral therapy to create a molecule which can downregulate viral gene expression.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using these ribozymes in vitro or in cells in culture, does not reasonably provide enablement for the use of these ribozymes in vivo in whole organisms. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of splicing target nucleic acid molecules in vivo, in order to alter the nucleic acid molecules within an organism. More specifically, The invention is currently drawn to a method of trans-splicing (and ribozyme used in this transplicing) using a ribozyme in a cell in which a deleterious RNA is corrected by splicing a new segment replacing the defective segment. The invention is is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass both in vivo and in vitro uses. The broad language expressly includes the use in organisms as demonstrated by the limitations to "in vivo" and "in vitro" in claims 5 and 6. This language therefore specifically includes

methods such as gene therapy for ribozyme introduction into the cell. The method broadly encompasses the use of the method in any cell type, in any tumor type, in any type of mammalian patient. Further, the cells undergoing the test may be subject to any of a variety of different conditions depending upon the particular patient studied, with insulin dependent patients, for example receiving daily doses of a compound which significantly alters cellular metabolism while cancer patients may be receiving chemotherapeutic treatments, pain medicine for surgery, corticosteroids to reduce trauma associated with surgery which themselves significantly impact cellular metabolism or any of a number of other complicating factors which impact the ability of the ribozyme to function and correct the defect.

Quantity of Experimentation

The quantity of experimentation in this area is large since there is significant variability in the efficacy of gene therapy. The amount of experimentation necessary to solve the problems associated with in vivo use of these ribozymes for gene therapy is very substantial, requiring extensive animal and human experimentation with numerous non-obvious improvements likely to be necessary in order to achieve functionality, safety and efficacy of the compound in an in vivo, organismal setting. This effort is an inventive, unpredictable and difficult undertaking in itself, and efficacy of ribozymes in gene therapy type procedures as a control would need to be demonstrated in a variety of different cell type models. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

There is abundant prior art to suggest that gene therapy is difficult, unpredictable and unsuccessful. A recent review by Rossi (TIBTECH (1995) 13:301-305) details a variety of problems seen in expression and targeting of ribozymes. Rossi, who is aware of the invention as published in the Nature paper, states,

"There are five critical areas of investigation that could lead to an increase in the efficacy of intracellular ribozymes. These are: (1) the delivery of ribozymes to the appropriate cells; (2) the efficient expression of ribozymes in these cells; (3) the co-localization of ribozymes in the same intracellular compartment as the targeted substrate RNA; (4) the specificity of the ribozyme to recognize and cleave only its target substrate RNA; and (5) the enhancement of ribozyme-mediated substrate turnover. Strategies for intracellular ribozyme applications that address current obstacles in these areas are likely to lead to successful applications for ribozymes (page 301, column 2, last paragraph to page 302, column 1, paragraph 1)".

This express statement shows that the prior art did not expect success in in vivo targeting of ribozymes. As of the filing date of the application, it was even less predictable and more experimental than shown by Rossi.

Working Examples

The specification has no working examples of in vivo treatment.

Guidance in the Specification.

The specification, while suggesting the use of the ribozymes in vivo, did not provide significant guidance on how to overcome art recognized problems in delivery of the riboyzmes in vivo.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, Rossi's explicit statement of the failure, even in August 1995, to enable the use of ribozymes in vivo as well as his awareness of the specific, claimed invention, along with the absence of working examples, the relatively small amount of guidance in the specification, the unpredictability in the art and the large amount of experimentation would be necessary to achieve function balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
6/29/05